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LEVOCETIRIZINE

A new selective H_1 receptor antagonist for use in allergic disorders

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CONTENTS

Summary

Levocetirizine is the active *R*-enantiomer of cetirizine and represents a new second-generation histamine H_1 antagonist. It has a high affinity and selectivity for H_1 receptors. Comparative studies have shown evidence of superior H_1 receptor binding affinity over its racemate, cetirizine. Levocetirizine has a favorable pharmacokinetic profile; it is rapidly and extensively absorbed, minimally metabolized, and has a lower volume of distribution (V_d) than some other second-generation antihistamines. A number of studies using the histamine-induced wheal and flare model have repeatedly demonstrated marked suppressive effects for levocetirizine. Levocetirizine has also been found to be effective in relieving symptoms of seasonal and perennial allergic rhinitis, including nasal congestion, and its side effects are minor.

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Introduction

Levocetirizine is a newly developed selective H_1 antagonist. It is the *R*-enantiomer or active isomer (eutomer) of the racemate cetirizine, a second-generation antihistamine. The less active *S*-enantiomer, or distomer, is dextrocetirizine (Fig. 1). There is no evidence of chiral inversion (*i.e.*, racemization) of levocetirizine in the body, a finding which is indicative of its stability (1, 2).

Available in several countries in Europe and in Asia, levocetirizine is marketed mainly under the

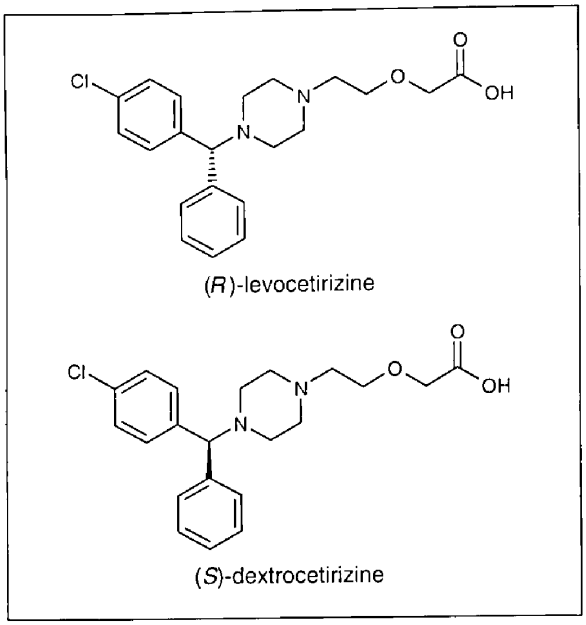

Fig. 1. Chemical structures of (*R*)-levocetirizine and (*S*)-dextrocetirizine.

trade names *Xyzal*® and *Xusal*® for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. This review will examine the pharmacology, therapeutic efficacy and safety of levocetirizine.

Pharmacology

Pharmacodynamics

Receptor binding

Levocetirizine is a competitive antagonist of histamine H_1 receptors (3) and is at least 600 times more selective for H_1 histamine receptors than for a variety of other G-protein-coupled receptors (4). Binding studies using cloned human H_1 receptors expressed in Chinese hamster ovary cells have shown that levocetirizine has a twofold higher affinity for H_1 receptors than cetirizine and an approximately 30-fold higher affinity than its enantiomer dextrocetirizine (5, 6). The carboxyl group of levocetirizine interacts strongly with the Lys^{191} residue of the human H_1 receptor, and this interaction is considered key to its long half-time of dissociation (6).

Histamine wheal and flare and nasal histamine challenge studies

A number of studies have confirmed levocetirizine to be the active enantiomer of cetirizine, and dextrocetirizine the inactive enantiomer. One study compared levocetirizine (2.5 mg) with cetirizine (5.0 mg) and dextrocetirizine (2.5 mg) using the histamine-induced nasal response model (7). Both levocetirizine and cetirizine significantly reduced sneezing and inhibited the histamine-induced increase in nasal airway resistance by nearly 50%, which was not observed with dextrocetirizine or placebo. In a study by Devalia *et al.* (8), the effects of these compounds were compared using the histamine-induced wheal and flare model in the skin. In this randomized, double-blind, crossover study using healthy volunteers, both cetirizine and levocetirizine produced a marked inhibition of histamine-induced wheal and flare, an effect not observed with dextrocetirizine. Inhibition by levocetirizine of both the wheal and flare responses was apparent in one hour, with inhibition of the wheal response lasting for a mean duration of 28.4 hours and with a maximal inhibition of 83.8% at 6 hours post-treatment. Inhibition of the flare response lasted a mean duration of 26.0 hours, with a maximal inhibition of 83.6% at 6 hours. While cetirizine produced similar inhibitory effects on these parameters, levocetirizine produced a greater effect than cetirizine on histamine-induced wheal from 0–32 hours postdose as calculated from the area under the curve (AUC, mean wheal area *vs.* time).

The effects of levocetirizine 5 mg were compared to those of loratadine 10 mg and placebo in terms of the wheal and flare response to intradermal histamine injection as well as subjects' self-rating of skin itch at 4 hours postdose (9). Levocetirizine significantly reduced flare, wheal and itch by 60%, 68% and 91%, respectively, while the effects of loratadine were variable and not significantly different from those of placebo. Another histamine-induced wheal and flare study compared levocetirizine 5 mg, ebastine 10 mg, fexofenadine 180 mg, loratadine 10 mg, mizolastine 10 mg and placebo in single doses (10). The overall effect of each drug was evaluated by the AUC for inhibition of wheal and flare over 24 hours. In this study, levocetirizine produced the greatest suppression of wheal and flare surface areas, followed by ebastine, fexofenadine and mizolastine—all of which had comparable effects. Loratadine produced the least suppression. A similar double-blind, randomized, crossover study involved 12 healthy volunteers who received a single dose of levocetirizine 5 mg, desloratadine 5 mg or placebo. When the AUC *versus* time for the wheal and flare response over 24 hours were compared, levocetirizine suppressed skin reactivity

to histamine to a greater degree, more consistently and for a longer duration than desloratadine (11). Another comparison of these same treatments in 18 healthy volunteers showed that levocetirizine and desloratadine were superior to placebo, and levocetirizine was superior to desloratadine. 'Total' wheal inhibition (≥95%) occurred only with levocetirizine, and the median duration of 70% wheal inhibition with this compound was 21.4 hours (12).

Antiallergic activity

Two *in vitro* studies have shown evidence of anti-inflammatory activity for levocetirizine. Michel *et al.* (13), using the skin chamber technique, found preliminary evidence that levocetirizine at therapeutic doses produces three main antiinflammatory effects: a decrease in eosinophil recruitment and a reduction in both soluble VCAM-1 release and protein levels affecting vascular permeability. Levocetirizine has also been found to inhibit eotaxin-induced eosinophil transendothelial migration (14).

Pharmacokinetics

Absorption

Levocetirizine undergoes rapid absorption, as evidenced by a maximal plasma concentration (0.27 ± 0.04 μg/ml) at 0.75 hours (t_{max}) following administration of a single oral dose of 5 mg of the ^{14}C-radiolabelled compound. Its extensive absorption is indicated by the recovery of 98.3% of the total radioactivity in the urine and feces at 168 hours (7 days) (2).

Distribution

Volume of distribution (V_d) is a proportionality factor relating the drug concentration in the blood or plasma to the total amount of drug in the body. It has been determined that the higher the degree of drug distribution and binding to tissue, the lower the concentration in the plasma, and thus the greater the V_d. Levocetirizine has been shown to have a low apparent V_d which has been estimated at 0.3–0.41 l/kg (1,2) and is believed to be attributable to its relatively high plasma protein binding (91.2%) (15, 16). Levocetirizine's V_d is lower than several other second-generation antihistamines, particularly loratadine and ebastine, both of which have a V_d estimated at >100 l/kg (17). A low V_d is desirable for medications in terms of both safety and efficacy since it indicates reduced exposure of organs which are not therapeutic targets to the circulating drug, thereby minimizing toxicity, the potential for drug–drug interactions and individual variations in therapeutic effect (16).

Levocetirizine's confinement to plasma is evidenced by a whole blood to plasma ratio of 0.51–0.68 during the first 12 hours following a single dose of [^{14}C]-levocetirizine, a finding indicative of minimal association with blood cells (2).

Metabolism and elimination

Levocetirizine is minimally metabolized; 85.8% of a single oral dose is excreted unchanged at 48 hours postdosing, with only 2.4% of the total dose comprised of metabolites (2). Notably, levocetirizine is not metabolized by CYP 2D6, a specific P450 isozyme that is commonly involved in drug–drug interactions (1). CYP 3A4, another P450 isozyme, metabolizes antihistamines such as terfenadine and astemizole. Co-administration of these antihistamines with potent inhibitors of CYP 3A4 (*e.g.*, ketoconazole, erythromycin) can lead to drug accumulation and adverse events (18). CYP 3A4 is unlikely to play a significant role in levocetirizine's restricted metabolism, but this has not been directly evaluated.

The half-life ($t_{1/2}$) of levocetirizine has been estimated at 7.05–7.8 hours (1, 2). Levocetirizine is largely eliminated by renal excretion; single oral administration of 5 mg [^{14}C]-levocetirizine to 4 healthy volunteers resulted in 85.4% of the total dose being recovered in the urine, while 12.9% was recovered in feces at 168 hours (7 days) postdose (2). Renal excretion of levocetirizine occurs by glomerular filtration and active tubular secretion, and renal clearance has been estimated at 29.2 ml/min (or 350 ml/min when corrected for protein binding). The nonrenal clearance of levocetirizine is relatively low (*i.e.*, 9.70 ml/min), which reduces its potential for metabolism-based drug interactions (1).

Therapeutic efficacy

Levocetirizine has been investigated for its efficacy in seasonal allergic rhinitis. Leynadier *et al.* (19) compared 2.5, 5 and 10 mg of levocetirizine and placebo administered once daily for 2 weeks during either grass or weed pollen season in France and Germany. In this study, 470 patients self-rated their symptoms of sneezing, rhinorrhea, nasal congestion, nasal pruritus and ocular pruritus on a scale from 0–3 each evening by means of diary evaluation cards. The total four-symptom score (T4SS) was calculated by adding each of the individual scores,

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